found throughout the specification and, *inter alia*, in claims 1-24 as originally filed. Support for the new claims 52-54 can be found throughout the specification and, *inter alia*, at page 9, line 21 through page 10, line 22 of the present specification. Support for the new claims 57-60 can be found throughout the specification and, *inter alia*, at page 7, lines 26-29 of the present specification. Therefore, the above-described amendments do not introduce any new matter into the present application.

Information disclosure statement

An information disclosure statement with the PTO Form 1449 listing references 1-52 is enclosed herewith and Applicants respectfully request the Examiner to consider and make references 1-52 of record of the present application.

Specification

The Office Actions states that the disclosure is objected to because of the following alleged informalities: page 5, line 14, "6" should be --5--; page 8, line 28, --immunogen-- is misspelled. The Office Actions states that appropriate correction is required.

This objection is overcome by the amendments at page 5, lines 14-15 and at page 8, lines 28-30. In addition, the paragraph of lines 12-22 at page 10 is also amended to correct typographical errors.

Sequence listings

The Office Actions states that this application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR § 1.821(a)(l) and (a)(2). It is alleged that this application clearly fails to comply with the requirements of 37 CFR §§ 1.821 through 1.825 for the reasons set forth below.

According to the teleconferences between the Examiner and the undersigned, it is the undersigned's understanding that Amendments submitted previously regarding the alleged sequence listing errors have been received and entered by the Patent Office. However, if the

undersigned's understanding is incorrect or if there is still error(s) in the sequence listing, Applicants will file another amended sequence listing upon receiving such a notice.

Rejection under 35 U.S.C. § 112

Claims 1-24 are rejected under 35 U. S. C. 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

It is alleged that:

- In claims 1-3, "the initial peptide" and "the reactive portion" lack antecedent basis.
- In claims 4-11, "the amount", "the initial peptide", and "the reactive portion" lack antecedent basis. Method claims should conclude with a step relating the method result to the purpose of the method, preferably to the purpose as also set forth in the preamble of the claim.
- In claims 5-6, "parathyroid...antibody" is confusing. The Examiner suggests --anti-parathyroid.. .antibody--.
- In claims 7-9 and 11, "wPTH" and "the first antibody" are not clear and lack antecedent basis.
- In claim 1 0, "the label or signal generating component" lacks antecedent basis.
- In claim 11, "the C-terminal portion" lacks antecedent basis and is vague as to what "portion" is encompassed. The interrelationships among the antibodies and their addition to sample is not clear. Method claims should clearly set forth the various method steps in a positive, sequential manner using active tense verbs such as adding, mixing, reacting, and detecting.
- In claims 12-16, "the amount", "the initial peptide", and "the reactive portion" lack antecedent basis. Method claims should conclude with a step relating the method result to the purpose of the method, preferably to the purpose as also set forth in the preamble of the claim.
- In claims 15-16, "the mid-portion" and "the C-terminal" lack antecedent basis and are vague as to what "portions" are encompassed. In these claims, the interrelationships among the antibodies and their addition to sample is not clear. It is also not clear how "whole" PTH is detected in such an assay as the binding to the N-terminus appears to

serve no function and label would bind and precipitate with other fragments bound by the third antibody such as the non-(1-84) PTH fragment.

- In claim 16, "C-terminal...antibody" is confusing. The Examiner suggests --anti-C-terminal...antibody--.
- In claim 17, "the initial peptide" and "the reactive portion" lack antecedent basis. Method claims should conclude with a step relating the method result to the purpose of the method, preferably to the purpose as also set forth in the preamble of the claim.
- In claims 18-19, "the initial peptide" and "the reactive portion" lack antecedent basis.
- In claim 19, "the C-terminal portion" lacks antecedent basis and is vague as to what "portion" is encompassed.
- In claims 20-21, "the initial peptide" and "the reactive portion" lack antecedent basis.
- In claim 21, "the C-terminal portion" lacks antecedent basis and is vague as to what "portion" is encompassed.
- In claim 22, "the amount", "the initial peptide", "the reactive portion", "the peptide sequence" lack antecedent basis. Method claims should conclude with a step relating the method result to the purpose of the method, preferably to the purpose as also set forth in the preamble of the claim.
- In claim 23, it is unclear from where "in the person" the levels are determined. Method claims should conclude with a step relating the method result to the purpose of the method, preferably to the purpose as also set forth in the preamble of the claim.
- In claim 24, "the person" lacks antecedent basis and it is unclear from where "in the person" the levels are determined. Method claims should conclude with a step relating the method result to the purpose of the method, preferably to the purpose as also set forth in the preamble of the claim.

These rejections are overcome by the replacement of claims 1-24 with claims 25-60, wherein the alleged errors no longer exist.

It is respectfully submitted that the rejections of claims 1-24 under 35 U.S.C. § 112 are overcome by the above amendments and must be withdrawn.

Rejections under 35 U.S.C. § 102

Claims 23-24 are rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Brossard et al., *J. Clin. Endocrinol. Metab.*, 81:3923 (1996)) ("Brossard"). Brossard is alleged to disclose determining levels of total parathyroid hormone (PTH) by two-site immunoassay and the proportions of that total comprising intact PTH-(1-84) and a non-(1-84) PTH fragment (by combination of high performance liquid chromatography (HPLC) with the immunoassay) in normal patients and two populations of patients having renal failure (with and without secondary hyperparathyroidism) under various calcemic conditions and compared the determinations within and among the patient populations by percentages and ratios. Brossard is also alleged to disclose that PTH determination in renal failure is of unquestioned clinical interest and that immunoassays have greatly simplified its measurement (see e.g. page 3923).

This rejection is rendered moot by the cancellation of claims 23-24. Brossard does not anticipate new claims 51-56 and 60 because Brossard does not disclose each and every element of claims 51-56 and 60. Claims 51-56 and 60 require the use of a substantially pure antibody or antibody fragment specific for an initial peptide sequence of whole parathyroid hormone which comprises VAL-SER-GLU-ILE-GLN-LEU-MET (SEQ ID NO:1), wherein at least four amino acids in said initial peptide sequence are part of a reactive portion with said antibody to measure whole parathyroid hormone level in said person, while not detecting an interfering non-(1-84) parathyroid hormone fragment. In contrast, the HPLC analysis disclosed in Brossard shows that the PTH immunoassay, *i.e.*, the I-PTH assay, is not capable of measuring whole parathyroid hormone level while not detecting an interfering non-(1-84) parathyroid hormone fragment.

It is respectfully submitted that the rejection of claims 23-24 under 35 U.S.C. § 102 is overcome by the above remarks and/or amendments and must be withdrawn.

Rejections under 35 U.S.C. § 103

LePage

Claims 1-4, 6-21, and 23-24 are rejected under 35 U.S.C. § 103(a) as being allegedly unpatentable over LePage et al., *Clin. Chem.*, 44:805 (1998)) (LePage). LePage is alleged to:

- use two-site immunoassays combined with HPLC to determine intact PTH and the non-(1-84) PTH fragment and to characterize the non-(1-84) PTH fragment in uremic

patient sera as similar, if not identical, to the commercially available PTH-(7-84) fragment,

- suggest that the non- (1-84) PTH fragment is devoid of at least some of the N-terminal amino acid residues necessary for the adenylate cyclase activation activity of the intact PTH-(1-84),
- teach that the amino-terminal antibodies in the commercially available immunoassay kits used in the reference for intact PTH are specific for epitopes in the region of amino acid residues 14-34 of PTH (thus the cross-reactivity of the assays with the non-(1-84) PTH fragment and the ability of these assays to detect the fragment in patient sera in the reference),
- suggest that the fragment retains the ability to bind to PTH receptors, and suggest that a "truly" intact PTH-(1-84) could be developed using antibodies expected to be elicited by the N-terminal portion of the intact PTH-(1-84) (see e.g. page 808, col. 1-2).

The Office Action concludes that it would have been obvious to one of ordinary skill in the art at the time the instant invention was made to have elicited antibodies to the N-terminal portion of the intact PTH-(1-84), particularly to amino acid residues 1-6, for use in determining the intact PTH and/or non-(1-84) PTH fragment in immunoassays for analysis of PTH in uremic patients in view of the specific suggestion and expectation of success provided for such antibodies and assays in LePage. It is alleged that substitutions of conventional alternatives for those particulars taught in the reference, such as substitution of a conventional alternative label, or using any of the conventional alternative reagent addition sequences, such as forward, reverse, or simultaneous, for a two-site immunoassay, or using the conventional alternative of a labeled anti-C-terminal antibody with an immobilized anti-N-terminal antibody instead of immobilized anti-C-terminal antibody and labeled anti-N-terminal antibody in a two-site immunoassay, would have been well within the skill of a routineer in the art and would have been expected to function in the assays suggested in the reference for determination of "truly" intact PTH- (1-84) and/or in assays to discriminate intact PTH from the non-(1-84) PTH fragment. It is also alleged that one would have been motivated to have provided such antibodies and assays to obviate the step of HPLC in the determinations. It is further alleged that it would have been obvious to formulate the reagents of LePage into a kit since that is conventional for convenience, economy,

and reproducibility. The Office Action concludes that the claimed invention as a whole was clearly prima facie obvious, especially in the absence of evidence to the contrary.

This rejection is rendered moot by the cancellation of claims 1-24. In addition, LePage does not render the presently claimed invention obvious for the following reasons. First, there is no motivation, whether explicitly or implicitly, to modify the teachings of LePage to arrive at the presently claimed methods and kits. As acknowledged by the Office Action, LePage uses HPLC, not immunoassay, to distinguish whole parathyroid hormone from the non-(1-84) parathyroid hormone fragment. The logic followed by the Office Action seems to be that since LePage teaches that the non-(1-84) parathyroid hormone fragment is 7-84 of the parathyroid hormone, it would be obvious to raise antibodies against the N-terminal region of the parathyroid hormone to replace the HPLC procedure with an immunoassay. This logic, however, is based on the assumption that LePage definitively teaches that the non-(1-84) parathyroid hormone fragment is 7-84 of the parathyroid hormone or a parathyroid hormone lacking a number of N-terminal amino acid residues. The problem is that this assumption is erroneous and LePage does not definitively teach that the non-(1-84) parathyroid hormone fragment is 7-84 of the parathyroid hormone or a parathyroid hormone lacking a number of N-terminal amino acid residues.

The only experimental data to support the position that the non-(1-84) parathyroid hormone fragment is 7-84 of the parathyroid hormone or a similar peptide is that the "minor peak" detected in the HPLC procedure of LePage migrates "before hPTH(1-84) and just ahead of hPTH(7-84)." (See LePage at 807, left column and Figure 2). It is well known in the art that comigration, even a complete comigration on HPLC, does not provide a conclusive answer as to whether the test substance is identical to the control substance. Here, all that has been shown is that the non-(1-84) parathyroid hormone fragment migrates between hPTH(1-84) and hPTH(7-84) and this cannot conclusively establish the identity of the non-(1-84) parathyroid hormone fragment at all. LePage recognizes this uncertainty itself; for LePage never states that the non-(1-84) parathyroid hormone fragment is 7-84 of the parathyroid hormone or a similar peptide. Rather, LePage always proposes this as a mere possibility to be further studied. For example, at page 807, right column, LePage states:

> To gain a better understanding of these differences, we next analyzed the immunoreactivity of hPTH(1-84) and hPTH(7-84), a commercially available molecule potentially structurally related to the non-(1-84)PTH peak (emphasis added).

Similarly, when discussing why the PTH assays studied therein did not distinguish between whole parathyroid hormone from the non-(1-84) parathyroid hormone fragment, LePage states:

> Although they were purified by affinity chromatography, the polyclonal antibodies used as signal and capture antibodies in the three assays theoretically have the ability to react with hPTH fragments lacking a small number of amino acids at either end of the PTH molecule (emphasis added).

These statements demonstrate clearly that LePage does not teach conclusively what the non-(1-84) parathyroid hormone fragment is. At best, LePage speculates about the identity of the non-(1-84) parathyroid hormone fragment and this speculation cannot be used as a motivation to modify its teachings to arrive at the presently claimed methods and kits.

Second, even assuming *arguendo*, that there is motivation in LePage to modify its teachings to arrive at the presently claimed methods and kits, such modification still does not teach all the elements of the presently claimed invention. As discussed above, the presently pending claims 25-60 require the use of a substantially pure antibody or antibody fragment specific for an initial peptide sequence of whole parathyroid hormone which comprises VAL-SER-GLU-ILE-GLN-LEU-MET (SEQ ID NO:1), wherein at least four amino acids in said initial peptide sequence are part of a reactive portion with said antibody to measure whole parathyroid hormone level in said person, while not detecting an interfering non-(1-84) parathyroid hormone fragment. LePage simply does not teach or suggest the use of an antibody with the presently claimed specificity to measure whole parathyroid hormone level in said person while not detecting an interfering non-(1-84) parathyroid hormone fragment. That is even assuming *arguendo*, that there is motivation in LePage to generate an antibody that specifically binds to the N-terminal region of hPTH, such a general teaching still does not teach an antibody used in the presently claimed methods and kits, *i.e.*, antibodies that specifically bind to whole parathyroid hormone or fragment that comprises a domain of 2-8 of hPTH and the antibodies must bind with at least 4 amino acid residues within the domain.

In this regard, it is worthwhile to point out that, in contrast to the Office Action's suggestion, LePage never teaches that the non-(1-84) parathyroid hormone fragment is 7-84 of the parathyroid hormone or that an antibody specific for 1-6 of hPTH should be generated.

Instead, LePage is very vague about the desired specificity of such antibodies or if such antibodies can actually be generated. For example, at page 808, right column, LePage states:

> Because there is no prima facie reason to think that antibodies to the endmost N-terminal portion of PTH cannot be generated, the development of a "truly" I-PTH assay remains a desirable goal (emphases added).

LePage does not further delineate what the "endmost N-terminal portion of PTH" is. Out of all the possibilities, there is no express teaching in LePage about the endmost N-terminal portion of PTH being 2-8 of the hPTH (*See* MPEP 2144.08, one should consider if there is express teaching in the prior art reference of a particular reason to select the claimed species or subspecies if the prior art reference teaches a genus). In addition, the antibody used in the presently claimed methods and kits must bind with at least 4 amino acid residues within the specified hPTH domain. There is certainly no teaching or even any suggestion on this aspect in LePage.

Therefore, the element of "a substantially pure antibody or antibody fragment specific for an initial peptide sequence of whole parathyroid hormone which comprises VAL-SER-GLU-ILE-GLN-LEU-MET (SEQ ID NO:1), wherein at least four amino acids in said initial peptide sequence are part of a reactive portion with said antibody to measure whole parathyroid hormone level in said person, while not detecting an interfering non-(1-84) parathyroid hormone fragment" is missing from LePage and this missing element can only be found in the present application. However, the teachings of the present application cannot be combined with prior art to render the presently claimed invention obvious ("To imbue one of ordinary skill in the art with knowledge of the invention in suit, when no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher." *W.L. Gore & Associates, Inc. v. Garlock Inc.*, 721 F.2d 1540, 1553, 220 USPQ 303, 312-13 (Fed. Cir. 1983)).

LePage and Campbell

Claims 1-21 and 23-24 are rejected under 35 U.S.C. § 103(a) as being allegedly unpatentable over LePage in view of Campbell. The Office Action acknowledges that teachings of LePage differ from the invention as instantly claimed in not providing monoclonal antibodies. Campbell is alleged to teach the general procedure for the production of monoclonal antibodies

(pages 3-6) and that substituting a monoclonal antibody for a polyclonal antibody in an established immunoassay "is not novel and is obvious" (page 45).

The Office Action concludes that it would have been obvious to one of ordinary skill in the art at the time the instant invention was made to have elicited monoclonal antibodies to the N-terminal portion of the intact PTH-(1-84), particularly to amino acid residues 1-6, for use in LePage et al because, as taught in Campbell, the substitution of monoclonal antibodies for polyclonal antibodies in an immunoassay is obvious in the art motivated by, inter alia, the well known advantage of providing a potentially unlimited source of homogeneous reagent. The Office Action also concludes that the claimed invention as a whole was clearly prima facie obvious, especially in the absence of evidence to the contrary.

This rejection is rendered moot by the cancellation of claims 1-24. In addition, LePage, even in combination with Campbell, does not render the presently claimed invention obvious because Campbell does not cure the defects of LePage. As discussed above, there is no motivation, whether explicitly or implicitly, to modify the teachings of LePage to arrive at the presently claimed methods and kits. Campbell also does not cure this defect because Campbell generally teaches techniques for generating monoclonal antibodies and is not specifically related to anti-PTH antibodies at all. LePage does not teach the requisite element of "a substantially pure antibody or antibody fragment specific for an initial peptide sequence of whole parathyroid hormone which comprises VAL-SER-GLU-ILE-GLN-LEU-MET (SEQ ID NO:1), wherein at least four amino acids in said initial peptide sequence are part of a reactive portion with said antibody to measure whole parathyroid hormone level in said person, while not detecting an interfering non-(1-84) parathyroid hormone fragment." Campbell also does not cure this defect because Campbell does not teach any anti-PTH antibodies.

Gao and LePage

Claims 1-5, 7-10, 12-14, 17, 18, 20 and 22 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Gao et al., *Clinica Chimica Acta*, 245:39 (1996)) (Gao) in view of LePage. Gao is alleged to teach a two-site immunoassay using monoclonal antibodies for detection of "intact" and large, biologically active, N-terminal fragments of PTH. The Office Action acknowledges that Gao differs from the invention as instantly claimed in not teaching the epitopes as instantly claimed for the two antibodies of the method.

Nevertheless, the Office Action concludes that it would have been obvious to one of ordinary skill in the art at the time the instant invention was made to have elicited antibodies to the N-terminal portion of the intact PTH-(1-84), particularly to amino acid residues 1-6, for use in determining the intact PTH and large N-terminal PTH fragments in the immunoassays of Gao in combination with antibodies to any other non-interfering N-terminal epitope in view of the specific suggestion and expectation of success provided for such N-terminal antibodies and assays in LePage. It is alleged that substitutions of conventional alternatives for those particulars taught in the reference, such as substitution of a conventional alternative label, or using any of the conventional alternative reagent addition sequences, such as forward, reverse, or simultaneous, for a two-site immunoassay, or using the conventional alternative of a labeled second anti - PTH antibody with an immobilized anti - N -terminal antibody instead of immobilized second anti-PTH antibody and labeled anti-N-terminal antibody in a two-site immunoassay, would have been well within the skill of a routineer in the art and would have been expected to function in the assays suggested in the references for determination of "truly" intact PTH-(1-84). It is also alleged that one would have been motivated to have provided such antibodies and assays to determine functionally active intact PTH and N-terminal fragments as desired by Gao. It is further alleged that it would have been obvious to formulate the reagents of Gao as modified by LePage into a kit since that is conventional for convenience, economy, and reproducibility.

This rejection is rendered moot by the cancellation of claims 1-24. In addition, LePage, even in combination with Gao, does not render the presently claimed invention obvious because Gao does not cure the defects of LePage. As discussed above, there is no motivation, whether explicitly or implicitly, to modify the teachings of LePage to arrive at the presently claimed methods and kits. Gao does not cure this defect. If anything, Gao teaches away from the presently claimed methods and kits because Gao teaches a PTH assay that does not distinguish whole parathyroid hormone from the non-(1-84) parathyroid hormone fragment. As taught at page 48 of Gao, Gao obtained a good agreement in normal volunteers, hyperparathyroidism patients and dialysis patients between its assay and Nichols' I-PTH assay (See also Figure 4 on page 49). LePage, of course, shows that Nichols' I-PTH assay cannot distinguish whole parathyroid hormone from the non-(1-84) parathyroid hormone fragment.

LePage does not teach the requisite element of "a substantially pure antibody or antibody fragment specific for an initial peptide sequence of whole parathyroid hormone which comprises VAL-SER-GLU-ILE-GLN-LEU-MET (SEQ ID NO:1), wherein at least four amino acids in said initial peptide sequence are part of a reactive portion with said antibody to measure whole parathyroid hormone level in said person, while not detecting an interfering non-(1-84) parathyroid hormone fragment." Gao does not cure this defect because the anti-PTH antibodies used in Gao also cannot distinguish whole parathyroid hormone from the non-(1-84) parathyroid hormone fragment.

The presently claimed invention is also not obvious in view of Brossard, LePage, Campbell and Gao because the presently claimed invention provides numerous unexpected benefits as discussed in detail in the Declaration of Dr. Ping Gao, which was submitted with the February 7, 2001 Amendment.

It is respectfully submitted that the rejections of claims 1-24 under 35 U.S.C. § 103 are overcome by the above remarks and/or amendments and must be withdrawn.

Double patenting rejection

Claims 23-24 are provisionally rejected under the judicially created doctrine obviousness type double patenting as allegedly being unpatentable over claims 7, 10, 31 and 44 of the copending Application Serial No. 09/344,639.

As stated in the February 7, 2001 Amendment, the present application and the cited one are co-owned. A terminal disclaimer will be submitted once allowable subject matter is indicated.

CONCLUSION

Applicants submit that the rejections of claims 1-24 under 35 U.S.C. §§ 102, 103 and 112 have been overcome by the above remarks and/or amendments. Early allowance of the pending claims 25-60 are earnestly requested.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, Applicants petition for any required relief including extensions of time and authorizes the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this

document to **Deposit Account No. 03-1952** referencing docket no. 532212000600. However, the Assistant Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Respectfully submitted,

Dated: May 17, 2002

By: _____

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EXHIBIT A. VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the specification:

At page 5, please replace the paragraph of lines 14-15 with the following new paragraph:

FIGURE [6] 5 is a graph comparing a conventional I-PTH assay with the present wPTH assay for healthy normal persons with "normal" PTH values.

At page 8, please amend the paragraph of lines 28-30 as follows:

The [imrnunogen] immunogen is mixed with an equal volume of Freunds complete adjuvant which is a mixture of light mineral oil and inactivated mycobactcrium tuberculosis bacilli.

At page 10, please amend the paragraph of lines 12-22 as follows:

The present wPTH assay has been used in a clinical setting involving 245 persons. The group included 32 persons having normal healthy parathyroid glands, 52 patients with pathologically confirmed primary hyperparathyroidism (1^0 HPT), and 161 patients with chronic uremia who are undergoing dialysis on a continuous basis. FIGURE [9] 8 illustrates patient [differentating] differentiating results using the wPTH assay. A person having substantially normal parathyroid hormone function can be differentiated from one having hyperparathyroidism by measuring whole parathyroid hormone levels. Moreover, chronic uremia patients can be differentiated into two groups by measuring whole parathyroid hormone levels in the person and comparing them to normal values, namely, those having substantially normal active parathyroid hormone levels, and those having hyperparathyroidism (or secondary hyperparathyroidism).